REMARKS

Claims 1-4, 11-16, 23-25, 32-34 and 53-54 are pending in the present application and stand rejected as indicated in the Office Action Summary. No ground of rejection was given for claim 11, however. The Examiner indicates that the rejection is non-final because the rejection is applied to claims previously indicated as allowable. Applicants request confirmation of this status as explained in the Office Action, page 2, lines 5-6, in light of the indication in the Office Action Summary at box 2a, which apparently was marked in error. Applicants also request allowance of claim 11, for which no grounds for rejection were provided.

Claims 1-4, 12-13, 15, 23-24, 32-34 and 53-54 are rejected as obvious over the primary reference, Tisch et al. ("Tisch"), in view of Crawford et al. ("Crawford") and Altman et al. U.S. Patent No. 5,635,363 ("Altman"). Wong et al. ("Wong") also is cited as evidence. The Crawford and Altman references are newly cited.

The Action asserts that Tisch teaches administration of GAD peptides including SEQ ID Nos: 2-4 to NOD mice to inhibit diabetes development and, in the case of peptides comprising SEQ ID NO:3, prevention of insulitis progression. The Office does not assert that the peptides of SEQ ID NO:1, SEQ ID NO:2 or SEQ

ID NO:3 were administered by Tisch, only that larger peptides which contained this sequence were administered. The Office also concedes that Tisch does not disclose the MHC haplotype of the NOD mice and relies on Wong, which is asserted to evidence that NOD mice express I-A^{g7}. Importantly, Tisch does not teach isolated MHC class II complexes with any GAD peptide (Office Action at page 3, line 1).

Crawford is cited as teaching soluble recombinant MHC class II molecules with antigenic peptides attached to the beta chain. Multimers of these molecules are asserted to bind normal T cells and T cell hybridomas. The Altman patent is not discussed in the Action and no specific teachings of Altman are mentioned.

The Office concludes that it would have been obvious to construct the "combinations taught by Tisch using the method of Crawford." No combinations are asserted to be taught by Tisch, however. This reference relates to immunization of mice with peptide or a combination of peptides in incomplete Freund's adjuvant. It does not mention any complexes made with the peptides or even suggest that one should attempt this.

Crawford is cited as teaching the combination of an antigenic peptide with an MHC beta chain. Crawford, however, did not teach use of any GAD peptides or any autoimmunity antigens for use with these complexes. Such antigens, for example the GAD

peptides recited in the claims here, are known to be extremely poor binders. Because of this well-known phenomenon, the art of the time that this application was filed taught that GAD autoimmunity peptide MHC complexes may not exist *in vivo* and that no stable GAD class II complexes could be made. See the Declaration of Dr. Liu under 37 C.F.R. § 1.132, an inventor of this application.

To make out a *prima facie* case of obviousness against a claim, the Office must meet all three of the following criteria: (1) the cited references must teach or suggest all elements of the rejected claim; (2) the references or the prior art generally must provide specific motivation to combine or modify the teachings of the cited art to achieve the claimed invention; and (3) there must be a reasonable expectation of success for the combined art. M.P.E.P. § 2143. Failure to meet even one of these criteria is fatal to a showing of *prima facie* obviousness.

None of the cited references teach the claimed complex alone, as conceded by the Office. The primary reference, Tisch, is cited as disclosing peptides that "include" SEQ ID Nos: 2,3 and 4, and are referred to as "epitopes." SEQ ID NO:3 (GAD65 221-235) is not taught or suggested by Tisch. Tisch discloses GAD65 217-236, which overlaps the present SEQ ID NO:3, but provides no guidance, suggestion, or even the merest hint as to

the active portion of 217-236 or whether the specific truncation to SEQ ID NO:3 would be useful at all. Therefore, at least SEQ ID NO:3 is nonobvious over Tisch. Tisch also does not teach or suggest MHC class II complexes.

The Office relies on the secondary reference, Crawford, for teachings with respect to such complexes. Crawford does not provide a reasonable expectation that it would be possible to achieve the claimed stable complex when using GAD peptides, particularly in view of the wisdom in the art at the time this application was filed as discussed in the accompanying Declaration of Dr. Liu. Crawford does not teach or even suggest that GAD or autoimmunity peptides can be used with their methods, nor does Tisch or Altman. No reference teaches that the GAD65 peptides claimed here or any GAD peptides can bind to form a stable complex as recited in the present claims.

The art generally, at the time this application was filed, taught that autoantigen-specific complexes were extremely difficult to produce due to poor binding and short half-lives. As one of skill can appreciate, manuscripts reporting failure to achieve GAD complexes would be unlikely to be published. However, Applicants refer the Office to the response filed by Applicants August 9, 2005, and the references cited therein,

which are of record here, as well as the accompanying Declaration of Dr. Liu.

The skilled person would have been aware of the difficulties in preparing autoantigen-specific complexes of the type claimed here and of numerous failed attempts by others to achieve them. See, for example Carasco-Marin et al., *J. Immunol.* 156:450-458, 1996, and Carasco-Marin et al., *Res. Immunol.* 148(5):291-301, 1997, of record here.

First, Carasco-Marin et al., (1996) states, *inter alia*, that I-Ag7 molecules bind peptides poorly, have short half lives and have a very low propensity to form stable complexes with peptides (See, *inter alia*, page 450, second full paragraph and page 452, third and fourth full paragraphs). Furthermore, the discussion throughout the reference, for example, at page 456, left-hand column, emphasizes repeatedly that I-Ag7 molecules interact poorly with self peptides. Indeed, the study found no peptides that formed a long-lived or SDS-stable complex with I-Ag7, including GAD 524-543. See Carasco-Marin et al. (1996), Table IV. These same authors found that both I-Ag7 and DQ have decreased SDS stability. See Carasco-Marin et al., (1997), page 294, fourth full paragraph and Table II. These findings clearly support the skepticism of skilled artisans at that time, that MHC class II molecules could bind peptides such as GAD peptides to

form a stable molecular complex. Applicants submit that the art as a whole strongly teaches against any expectation of success for the stable complexes that are claimed here. Accordingly, the cited references, in light of the art as a whole, do not provide motivation to combine their teachings with any reasonable expectation of success in achieving the stable molecular complex of the claimed invention.

Applicants submit that the concurrently-submitted Liu Declaration supports the patentability of the present claims. In particular, Dr. Liu provides further evidence that no reasonable expectation of success was found in the art with respect to this invention at the time this application was filed. Dr. Liu's declaration is pertinent to the examination of the claims. This declaration shows that while MHC class II molecules and GAD peptides may have been known individually; there was no reasonable expectation of success for stable I-Ag7- or DQ-peptide complexes because the art taught that making and using such MHC class II complexes was unpredictable and risky. Accordingly, Applicants request that the Examiner consider the Declaration and the evidence it provides, in view of the above arguments.

In summary, Applicants respectfully submit that the cited references, alone or in combination, do not teach or suggest the claimed complexes and that there is no motivation to modify those

references with a reasonable expectation that stable GAD peptide-binding I-Ag7 or DQ complexes as claimed would be successful. Tisch discloses peptides only while Crawford fails to teach or suggest that the claimed GAD complexes could be formed. The art generally expresses doubt and skepticism regarding stable autoantigen complexes. The Office therefore cannot make out a proper *prima facie* case of obviousness against the claims here.

The Altman patent, which is listed in the rejection but not discussed, discloses MHC-antigen complexes. The art in general, however, teaches that stable MHC-GAD autoantigen complexes were not formed. Failure of others and the skepticism expressed by skilled persons at the time indicate that the invention was not obvious.

Applicants request reconsideration of the claims and withdrawal of the rejection over the combination of Tisch, Crawford and Altman.

Claims 14, 16 and 25 are rejected over Tisch in view of Crawford, Altman and Kendrick et al. (U.S. Patent No. 5,595,881; "Kendrick"). The lack of reasonable expectation of success should one of skill have attempted to achieve the claimed complexes is discussed above.

The Altman reference is not discussed here or above, but relates to MHC-antigen complexes. None of Altman, Tisch nor

Crawford, however, demonstrate that the GAD complexes of the claims actually are achievable. The vast weight of the art at the time this application was filed indicated that GAD autoimmune MHC complexes could not be formed with any stability because of the low affinity and avidity of the binding of such autoimmune peptides which caused an extremely short half-life of occupation in the binding cleft of the complex. See accompanying Declaration of Dr. Liu.

Kendrick also relates to MHC-antigen complexes and is cited for teachings pertaining to oligohistidine tags. Kendrick also fails to provide a working example, or other indication that the GAD complexes of this invention actually can be achieved. In view of the art generally, which teaches that stable complexes, as claimed here and achieved for the first time by the inventors, could not be produced, Applicants submit that the Office cannot make out a *prima facie* case of obviousness using any combination of the cited references because there would have been no reasonable expectation of success. Furthermore, even if one assumes that the Office can make out a *prima facie* case, this is overcome by the evidence of nonobviousness in the art generally at the time. This includes failure of others and skepticism in the art.

Applicants therefore request withdrawal of the rejection based on obviousness over Tisch, Crawford, Altman and Kendrick and reconsideration of the claims.

Applicants respectfully request that the application proceed to allowance at this time.

RESPECTFULLY SUBMITTED,					
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